II. REMARKS/ARGUMENTS

A. Status of Claims

Claim 38, 47, 49, 50, 51, and 52 have been amended without prejudice. Support for the amendments can be found throughout the specification, e.g., on page 23, line 4, to page 30, line 15, and on page 22, lines 5-22, of the original specification.

New claims 53-65 have been added. Support for new claims 53 and 54 can be found, e.g., in original claims 38, 49 and 50; and on page 24, line 31, to page 25, line 31, of the original specification. Support for new claims 55 and 60 can be found, e.g., on page 34, lines 11-23, of the original specification. Support for new claim 56 can be found, e.g., on page 22, lines 5-22, of the original specification. Support for new claims 57 and 58 can be found, e.g., on page 25, lines 16-17, of the original specification. Support for new claim 59 can be found, e.g., on page 11 of the original specification. Support for new claim 61 can be found, e.g., on page 38, line 31, of the original specification. Support for new claims 62-65 can be found, e.g., in original claims 38, 47, 49, and 50.

Claims 1-37 and 39-46 were previously cancelled without prejudice.

Claims 38 and 47-65 are currently pending.

Applicants respectfully submit that no new matter has been added by virtue of these amendments.

B. Rejection under 35 U.S.C. 103 (a) over Baker et al. and Tanaka et al.

In the Office Action, claims 38, 47-48 and 50-52 were rejected under 35 U.S.C § 103(a) over US 4,569,937 (hereinafter "the Baker patent") and Tanaka et al. Arzneimittel-Forschung (1992) Vol. 42 (7) pages 935-44 (hereinafter "the Tanaka reference").

Claim 38 has been amended without prejudice to recite:

> 38. A method of effectively treating pain in humans, comprising orally administering to a human patient an oral dosage form **consisting of**
>
> (i) N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide or at least one pharmaceutically acceptable salt thereof;
>
> (ii) oxycodone and/or at least one pharmaceutically acceptable salt thereof; and
>
> (iii) at least one pharmaceutically acceptable excipient;
>
> **wherein said pain is cancer pain, post-surgical pain, low back and neck pain, dysmenorrheal, headache, toothache, pain from sprains and strains, myositis, neuralgia, synovitis, arthritis, degenerative joint diseases, gout and ankylosing spondylitis, bursitis, burns, injuries, influenza or other viral infections, and common cold.**

(emphasis added).

Applicants respectfully submit that the combination of the cited references would not have suggested to one skilled in the art a method of treating pain, "wherein said pain is cancer pain, post-surgical pain, low back and neck pain, dysmenorrheal, headache, toothache, pain from sprains and strains, myositis, neuralgia, synovitis, arthritis, degenerative joint diseases, gout and ankylosing spondylitis, bursitis, burns, injuries, influenza or other viral infections, and common cold" as recited in the present claims, as none of the cited references mention "cancer pain, post-surgical pain, low back and neck pain, dysmenorrheal, headache, toothache, pain from sprains and strains, myositis, neuralgia, synovitis, arthritis, degenerative joint diseases, gout and ankylosing spondylitis, bursitis, burns, injuries, influenza or other viral infections, and common cold."

Further, Applicants respectfully submit that a dosage form suggested by the combination of the cited references would necessarily contain ibuprofen, because the purpose of the Baker

patent, entitled ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN and utilizing ibuprofen in every example, would be frustrated without ibuprofen.

Further, as noted by the Examiner, the Baker patent states that "unexpectedly enhanced analgesic activity of combination of oxycodone and ibuprofen" is the activity that is "**greater that the activity expected from the sum of the activities of individual components**" (i.e., a synergistic effect). See column 3, lines 22-26 (emphasis added).

In fact, Applicants submit that it is the "synergistic" effect that differentiated, inter alia, the purported invention of the Baker patent from the references described in the Background section of the Baker patent (i.e., references describing merely an additive effect). Applicants further submit that it is the "synergistic" effect that purportedly contributed, inter alia, to patentability of the Baker patent over these references (i.e., references describing merely an additive effect, and not a synergistic effect). Accordingly, Applicants submit that one skilled in the art, looking at the Baker patent as a whole, would conclude that the effect contemplated by the Baker patent is "synergistic," and not merely additive.

Applicants further submit that the Baker patent when considered as a whole would not have suggested to one skilled in the art looking to improve on the analgesic combination described therein a combination with a merely additive analgesic effect, as this would be a step back from the "synergistic" combinations described in the Baker patent.

Applicants submit that the "synergistic" combination in accordance with the Baker patent would necessarily include ibuprofen, at the very least because the only NSAID utilized in the invention of the Baker patent, the patent entitled ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN and utilizing ibuprofen in every example, is ibuprofen. See e.g., column 1, lines 6 - 9 ("[t]his invention relates to pharmaceutical compositions of narcotic analgesics and **ibuprofen** having analgesic activity in mammals, and to methods of use of the compositions to alleviate pain in mammals") (emphasis added); *see also* column 2, lines 11-15 ("[a]ccording to the present invention there is provided a pharmaceutical composition comprising a combination

of (a) a narcotic analgesic, or a pharmaceutically acceptable salt thereof, and (b) **ibuprofen**, or a pharmaceutically suitable salt thereof ... ") (emphasis added); *see also* Figure 1 ("ISOBOLOGRAM FOR THE INTERACTION OF ORAL OXYCODONE HCL AND **IBUPROFEN**") (emphasis added); *see also* column 1, line 1 & 2 ("ANALGESIC MIXTURE OF OXYCODONE AND **IBUPROFEN**") emphasis added; *see also* column 2, lines 20-24 (" ... synergistically effective analgesic amounts of oxycodone, or a pharmaceutically suitable salt thereof, and **ibuprofen**, or a pharmaceutically suitable salt thereof...") (emphasis added); *see also* column 2, line 34 and 35 ("... various dose ratios of oxycodone and **ibuprofen**); *see also* column 2, lines 64 and 65 ("[i]n a composition of the invention, oxycodone and **ibuprofen** are combined ...) (emphasis added); see also column 3, lines 23 and 24 ("... unexpectedly enhanced analgesic activity of combinations of oxycodone and **ibuprofen**") (emphasis added); *see also* column 3, lines 53-56 ("... the active ingredient is administered at a daily dosage of from about 0.05 to 7.50 milligrams per kilogram (mg/kg) of body weight of oxycodone and from about 10 to 120 mg/kg of **ibuprofen**") (emphasis added); *see also* Examples 1-24, all utilizing ibuprofen.

With regard to the Examiner's reference to column 1, lines 23-25, of the background section of the Baker patent where it is stated that "the analgesic effect of the combination of a selected NSAID and a selected analgesic is greater that for either alone," Applicants respectfully submit that this passage does not suggest a synergistic effect, but merely an additive effect, as acknowledged by the Examiner. See e.g., Office Action, page 3. As stated above, a merely additive effect is a step back from the synergistic combinations described in the Baker patent, and therefore, the Baker patent would not have suggested to one skilled in the art looking to improve the synergistic combinations of the Baker patent a combination that provides a merely additive effect, and not a synergistic effect as contemplated by the Baker patent.

Manual of Patent Examining Procedure states that "... [i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification") See, e.g., MPEP, Section 2143.01.

Applicants submit that ibuprofen is excluded from the scope of amended claim 38, by virtue of "consisting of" language.

Accordingly, Applicants submit that the combination of the cited references would not have suggested to one skilled in the art "an oral dosage form consisting of (i) N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide or at least one pharmaceutically acceptable salt thereof; (ii) oxycodone or at least one pharmaceutically acceptable salt thereof; and (iii) and at least one pharmaceutically acceptable excipient" as recited in amended claim 38, because the claimed dosage form excludes ibuprofen, and therefore, renders the Baker patent unsuitable for its intended purpose- i.e., pharmaceutical compositions of narcotic analgesics and ibuprofen exhibiting synergistic analgesic activity.

Applicants also submit that the combination of the cited references would not have suggested to one skilled in the art "an oral dosage form consisting of (i) N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide or at least one pharmaceutically acceptable salt thereof; (ii) oxycodone or at least one pharmaceutically acceptable salt thereof; and (iii) and at least one pharmaceutically acceptable excipient" as recited in the present claims, because none of the cited references teach or suggest "an oral dosage form consisting of (i) N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide or at least one pharmaceutically acceptable salt thereof; (ii) oxycodone or at least one pharmaceutically acceptable salt thereof; and (iii) and at least one pharmaceutically acceptable excipients" as recited in the present claims.

In response to the Examiner's statement that "[t]he Examiner is unaware of any *per se* rule that necessarily limits the teachings of a reference to its preferred "synergistic" embodiments or teachings to certain locations within the document itself," Applicants respectfully note that it is not the preferred embodiments or certain locations within the Baker patent that describe the "synergistic" combination, but the entire disclosure of the invention, with the exception of the Background of the Invention section. Applicants respectfully submit that the Applicants' interpretation of the reference is consistent with the requirement that "[t]he

reference must be considered as a whole ..." See, e.g., MPEP, section 2141 (II)(B); see also MPEP, Section 2141.02.

Further, Manual of Patent Examining Procedure states that

> *The examiner bears the initial burden of* ***factually*** *supporting any prima facie conclusion of obviousness. If, however, the examiner does not produce a prima facie case, the applicant is under no obligation to submit evidence of nonobviousness.*

See, MPEP, Section 2142. (emphasis added).

In the present case, the Examiner has not articulated what would have suggested to one skilled in the art to

(i) pick N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide out of, e.g., other COX-2 inhibitors having similar properties to N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide, and

(ii) disregard the teachings of the Baker patent and replace ibuprofen, the essential ingredient of the Baker patent combination, with N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide.

To the contrary, the Examiner stated that "[t]her's no evidence to suggest that Baker et al. knew anything about the benefits of T-614."

In particular, the Examiner has not articulated what would have prompted one skilled in the art to select N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide for inclusion in the combination with oxycodone instead of, e.g., "celecoxib (SC-58635), DUP-697, flosulide (CGP-28238), meloxicam, 6-methoxy-2 naphthylacetic acid (6-MNA), Vioxx (rofecoxib) (MK-966), nabumetone, nimesulide, NS-398, SC-5766, SC-58215 ..." and other COX-2 inhibitors in the development as of mid-1998, all regarded to have "a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding time and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic

subjects", as compared to traditional NSAIDs (e.g., ibuprofen) at the time the present application was filed. See e.g., page 13 of the present specification.

The Examiner has also not articulated what would have suggested to one skilled in the art to look to the Tanaka reference, and pick the Tanaka reference, instead of references directed to other COX-2 inhibitors, having similar properties to N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide, e.g., COX-2 inhibitors mentioned above.

Applicants further submit that MPEP states that "... Office personnel **must** articulate ... a finding that one of ordinary skill in the art would have recognized that the results of the combination were **predictable**." See MPEP, section 2143. (emphasis added).

Applicants respectfully submit that in order to for the one skilled in the art to even consider modifying the combination of the Baker patent by replacing ibuprofen with N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide in view of the cited references, the cited references would have to at least indicate that the combination of N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide and oxycodone would also result in a synergistic effect, as the effect contemplated by the combination of the Baker patent is synergistic for the reasons set forth above.

However, the cited references do not suggest that the analgesic effect of the combination of N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide and oxycodone would be synergistic. In fact, the Examiner himself stated that Baker et al. "realized the synergistic value of the combination" only after they combined the analgesics, "otherwise the result would not have been "unexpected" as purported." See Office Action, page 7.

Therefore, Applicants submit that the "synergistic" value was not predictable at the time of the Baker's invention, otherwise Baker et al. themselves would not have labeled the results "unexpected."

Accordingly, Applicants submit that the Examiner has not shown and articulated a finding that the results of the suggested combination (e.g., a synergistic analgesic effect) would be predictable to one skilled in the art, as required by the MPEP.

Applicants respectfully assert that, in the absence of these findings, the obviousness rejection is not factually supported enough to establish the *prima facie* case of obviousness. See, MPEP, Section 2142.

In the event the Examiner disagrees with Applicants' conclusion, Applicants respectfully request that the Examiner provides factual evidence (i.e., isobologram for the interaction of oral oxycodone and N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide) to support the position that the synergistic result would have been predictable to one skilled in the art.

Further, Applicants respectfully disagree with the Examiner's statement on page 8 of the Office Action that "[w]hether another analgesic combination would be "unexpectedly" better is immaterial," at the very least because "unexpectedly" rebuts an inference that results of the combination were predictable to one skilled in the art; and MPEP specifically states that "... Office personnel **must** articulate ... a finding that one of ordinary skill in the art would have recognized that the results of the combination were **predictable**." See MPEP, section 2143. (emphasis added).

Applicants also respectfully disagree with the Examiner's statement that "the facts of the instant case and the conclusion of obviousness made by the Examiner are somewhat similar to the facts and decision of Court in, Syngenta Seeds, Inc., v. Mosanto Co., (Fed. Cir. 2007), opinion decided on May 3, 2007." See Office Action page 8.

First, the patent at issue in the Syngenta case did not cover pharmaceutical formulations as recited in the present case, rather it covered transgenic corn plants.

Second, the obviousness rejection in the Syngenta case relied on a single reference (U.S. Patent Application No. 2001/00034849 to Barton), and not on a combination of references as in the present case.

Third, the limitation at issue in the Syngenta case was concerned with an amount of an element described in the cited reference (i.e., "wherein the foreign DNA nucleic acid coding sequence has a G+C content of at least 60%"), whereas in the present case the entire elements, not merely amounts of elements (i.e., N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide or "a combination of N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide and oxycodone"), are missing from the primary reference (i.e., the Baker patent).

Finally, the cited reference in the Syngenta case (i.e., the Barton application) itself contained a suggestion that an increased efficacy "**might still be expected** ...", even with a complete "codon substation." In contrast, in the present cases the Baker patent does not provide the required suggestion, as Baker et al. themselves label the result "unexpected," and, therefore, upredictable.

Accordingly, Applicants submit that the facts of the present case and the conclusion of obviousness made by the Examiner are not close to the facts and decision of Court in Syngenta case.

Applicants further submit that even if a *prima facie* case of obviousness has been established (a position which is traversed), the combination of the cited references still would not have suggested to one skilled in the art "an oral dosage form consisting of (i) N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide or at least one pharmaceutically acceptable salt thereof; (ii) oxycodone or at least one pharmaceutically acceptable salt thereof; and (iii) at least one pharmaceutically acceptable excipient" as recited in the present claims, because the proposed modification would render the Baker patent unsuitable for its intended purpose for the reasons set forth above. See, e.g., MPEP, Section 2143.01 ("[i]f

proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification ...").

Accordingly, withdrawal of the rejection of claim 38 and claims 47-48 and 50-52 which depend therefrom is respectfully requested.

In the event, the Examiner seeks to maintain the rejection based on the combination of the cited references, Applicants respectfully request that the missing reasons and evidence (as pointed out above) be provided to factually support the rejection as required by the MPEP, and to allow Applicants to properly evaluate the basis for the Examiner's positions and respond appropriately. See, MPEP, Section 2142.

C. Rejection under 35 U.S.C. 103 (a) over Baker et al. and Tanaka et al. in view of Oshlack et al. (US 5,472,712) or Oshlack et al. (US 6,294,195)

In the Office Action, claim 49 was under U.S.C. § 103(a) over Baker patent and the Tanaka reference in view of US 5,472,712 (Oshlack et al.) and US 6,294,195 (Oshlack et al.)

Claim 49 depends from claim 38. Claim 38 was discussed above.

Applicants submit that, for the reasons discussed above, the combination of the cited references would not have suggested to one skilled in the art "an oral dosage form consisting of (i) N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide) or at least one pharmaceutically acceptable salt thereof; (ii) oxycodone or at least one pharmaceutically acceptable salt thereof; and (iii) at least one pharmaceutically acceptable excipient" as recited in claim 38, because the proposed modification would render the Baker patent unsuitable for its intended purpose. See, e.g., MPEP, Section 2143.01. "... [i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification ...").

Accordingly, Applicants respectfully submit that claim 38 is not rendered obvious by the combination of the cited references.

Applicants submit that claim 49 which depends from claim 38, and includes the features of claim 38, is also not rendered obvious by the combination of the cited references. See, e.g., *In re Fine*, 837 F.2d. 1071 (Fed. Cir. 1988) ("Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious. *Hartness Int'l, Inc. v. Simplimatic Eng'g Co.,* 819 F.2d 1100, 1108, 2 USPQ2d 1826, 1831 (Fed.Cir.1987); *In re Abele,* 684 F.2d 902, 910, 214 USPQ 682, 689 (CCPA 1982); *see also In re Sernaker,* 702 F.2d 989, 991, 217 USPQ 1, 3 (Fed.Cir.1983)").

Accordingly, withdrawal of the rejection is respectfully requested.

III. CONCLUSION

An early and favorable action on the merits is earnestly solicited. The Examiner is respectfully requested to contact the undersigned at the telephone number provided below in the event that a telephonic interview will advance the prosecution of the application.

Respectfully submitted,
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